

# The antimanic-like effects of andrographolide and quercetin

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## SUMMARY

Increased activity of the enzyme glycogen synthase kinase 3 beta (GSK3 $\beta$ ) is shown to play a pivotal role in the pathophysiology of several psychiatric disorders, including bipolar disorder (BD). Lithium, the prototype mood stabilizer, is an inhibitor of GSK3 $\beta$ . In animal models of mania, GSK3 $\beta$  inhibitors reproduce behaviors that mimic the effects of lithium. The pharmacological management of BD consists of administration of mood stabilizers or antipsychotics associated to antidepressants and it often involves a myriad of adverse effects or non-responsiveness, which affect medication adherence and quality of life. The search for new therapeutic agents for BD is therefore necessary. Considering that the inhibition of GSK3 $\beta$  activity may display antimanic-like effects, we tested the effects of andrographolide (ANDRO), the major bioactive compound isolated from *Andrographis paniculata*, which is an inhibitor of GSK3 $\beta$ . Studies showed that ANDRO possesses several therapeutic properties, including anti-inflammatory, antioxidant, antibacterial, hepatoprotective, neuroprotective, among others. Both ANDRO and lithium have been shown to decrease GSK3 $\beta$  levels and increase the levels of p-Ser<sup>9</sup>-GSK3 $\beta$ , the phosphorylated and inactive form of GSK3 $\beta$ .

Taking into consideration that GSK3 $\beta$  is an enzyme involved in the pathophysiology of BD and that GSK3 $\beta$  inhibition, such as induced by lithium, ameliorates manic symptoms, the effects of the chronic treatment with the GSK3 $\beta$  inhibitor ANDRO were tested in different animal models of mania, such as sleep deprivation (SD)-, methylphenidate- and lisdexamfetamine (LDX)-induced hyperlocomotion, increases in 50-kHz ultrasonic vocalizations (USVs) and oxidative stress. We also evaluated the effects of ANDRO in the levels of GSK3 $\beta$  and p-Ser<sup>9</sup>-GSK3 $\beta$  in the prefrontal cortex (PFC) and striatum of mice. A summary of the results is given below.

SD resulted in hyperlocomotion and treatment with lithium, 0.5 mg/kg ANDRO, and 2.0 mg/kg ANDRO blocked SD-induced hyperlocomotion. SD decreased the p-Ser<sup>9</sup>-GSK3 $\beta$ /GSK3 $\beta$  ratio in the PFC. Both lithium and 2.0 mg/kg ANDRO increased the p-Ser<sup>9</sup>-GSK3 $\beta$ /GSK3 $\beta$  ratio in the PFC.

Methylphenidate administration increased locomotor activity compared to the control group and treatment with lithium, 0.5 mg/kg ANDRO, and 2.0 mg/kg ANDRO

blocked methylphenidate-induced hyperlocomotion. Methylphenidate reduced the p-Ser<sup>9</sup>-GSK3 $\beta$ /GSK3 $\beta$  ratio in the striatum. Both lithium and 2.0 mg/kg ANDRO increased the p-Ser<sup>9</sup>-GSK3 $\beta$ /GSK3 $\beta$  ratio in the striatum.

LDX increased locomotor activity in rats, which was prevented by chronic treatment with lithium or 2.0 mg/kg ANDRO. LDX administration increased the number of 50-kHz USVs, which was also prevented by chronic treatment with lithium or 2.0 mg/kg ANDRO. Lithium and 2.0 mg/kg ANDRO also prevented LDX-induced increases in lipid peroxidation (LPO), an oxidative stress parameter in the striatum. There was a positive correlation between LDX-induced hyperlocomotion and LDX-induced increases in 50-kHz USVs and LPO.

Both 10 and 40 mg/kg quercetin prevented SD-induced hyperlocomotion. Quercetin reversed the SD-induced decrease in glutathione (GSH) levels in the PFC and striatum. Quercetin also reversed the SD-induced increase in LPO in the PFC, hippocampus, and striatum. Pearson's correlation analysis revealed a negative correlation between locomotor activity and GSH in the PFC in sleep-deprived mice and a positive correlation between locomotor activity and LPO in the PFC and striatum in sleep-deprived mice.

Chronic but not acute treatment with quercetin (10 and 40 mg/kg) blocked methylphenidate-induced hyperlocomotion. Chronic treatment with lithium and quercetin blocked the methylphenidate-induced increase in LPO levels in the striatum.

Overall, the results show that chronic treatment with ANDRO prevented hyperlocomotion induced by SD and methylphenidate, while increasing the p-Ser<sup>9</sup>-GSK3 $\beta$ /GSK3 $\beta$  ratio in the PFC and striatum of mice, respectively. ANDRO also prevented LDX-induced hyperlocomotion and increases in the number of 50-kHz USVs, while also preventing LDX-induced LPO in the striatum of rats. Quercetin also prevented SD and methylphenidate-induced hyperlocomotion, while also preventing SD-induced decreases in GSH in the PFC and striatum, and LPO in the PFC, hippocampus and striatum. Quercetin also blocked methylphenidate-induced hyperlocomotion, and methylphenidate-induced increase in LPO levels in the striatum. Thus, both ANDRO and quercetin appears to possess antimanic-like effects and they are promising agents to be thoroughly investigated for the management of mania in BD.